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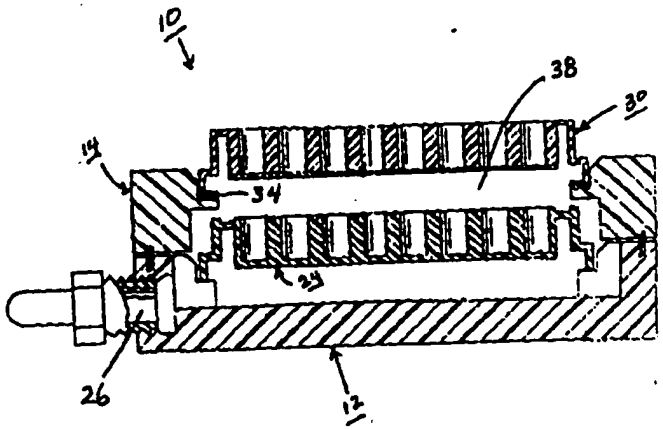
(54) Title: VACUUM MANIFOLD FOR LABORATORY PROCESSING OF MULTIPLE LIQUID SAMPLES

(57) Abstract

The invention provides a vacuum manifold which can be conveniently used in semi-automated and fully-automated laboratory machines to carry out a sequence of vacuum-assisted laboratory manipulations on a large number of individual liquid samples. The invention has a base (12) which is sized and dimensioned to accept and retain a first liquid receptacle (24), such as a microtitre dish. Generally, the base (12) has a bottom wall (16) and side walls (18) and the first receptacle (24) is designed to be retained within the side walls (18). The invention also has an adapter frame which is sized and dimensioned to accept and retain a second liquid receptacle (30), such as a second microtitre dish. The adapter frame (14) is typically a rectangular frame structure having a lip (32) which supports the second receptacle (30). The base (12) generally has a port (26) which is attachable to a source of vacuum. In operation, the first liquid receptacle (24) is placed within the base (12), the adapter frame (14) is placed on top of the base (12) and the second liquid receptacle (30) is placed on the adapter frame (14) so that a second receptacle (30) is located directly above the first receptacle (24). When vacuum is applied to the base using the vacuum port (26), a uniform vacuum is drawn along the bottom of the second liquid receptacle (30) which provides a driving force which acts upon liquid within the second receptacle (30). In a typical operation, the bottom of the second receptacle (30) is a filtration membrane and the vacuum is used to draw liquid from the second receptacle (30) across the filtered membrane into the first receptacle (24). Because of its modular construction, the various elements of the vacuum frame are easily stacked in stacking frames disposed to one side of the vacuum manifold. This stacking capability allows a large number of vacuum-assisted laboratory operations to be carried out on multiple sets of liquid samples without the necessity of a large amount of horizontal lab bench area. The stacking capability also facilitates the adaption of the invention with robotic equipment to provide a fully-automated laboratory processing tool.



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VACUUM MANIFOLD FOR LABORATORY PROCESSING OF MULTIPLE LIQUID SAMPLES

FIELD OF THE INVENTION

This invention relates generally to vacuum manifold devices, and specifically, to vacuum manifold devices useful in the simultaneous laboratory processing of multiple liquid samples.

BACKGROUND

It has become a common practice in testing laboratories to carry out simple laboratory processing steps on multiple liquid samples at the same time, in a single apparatus. This practice has greatly increased the efficiency of testing laboratories, especially laboratories doing a large volume of routine test work.

The simultaneous testing of multiple liquid samples in a single apparatus is conducted with apparatus especially designed for this purpose. The most common piece of apparatus is a disposable tray having multiple individual

"wells." These trays, commonly called "microtitre dishes," are made by a large number of manufacturers in a variety of sizes and shapes. In practice, an individual liquid sample is placed within each of the wells, where it is manipulated as part of the testing process.

Recently, equipment manufacturers in the trade have begun marketing specially designed vacuum manifolds for use with microtitre dishes. Such manifolds allow the practitioner to carry out common laboratory processes in microtitre dishes using vacuum as assisting force. Examples of such practices are filtration, drying and chromatography processes.

Unfortunately, the vacuum manifolds presently useful with microtitre dishes are not completely satisfactory. One problem is that such prior art vacuum manifolds are designed to work with specific microtitre dishes of a particular size and shape. If a practitioner wishes to another his microtitre dish, one with a different height or "footprint," the practitioner must invest in another vacuum manifold, one designed specifically for such other microtitre dish.

Another problem arises from the fact that vacuum processes generally constitute only one of several other processes which any particular liquid sample is to be subjected to. Handling the microtitre dishes from one testing operation to another frequently takes up a great deal of laboratory bench area as the various microtitre dishes are set aside between process steps.

A third problem is that, because of the relative inflexibility of present-day vacuum manifolds, and the excessive amount of area required by present-day multiple testing operations, present-day vacuum manifolds are not

easily incorporated into fully automated machines capable of carrying out a multiplicity of laboratory procedures using a relatively small amount of work space.

Accordingly, there is a need for a vacuum manifold which can simply, conveniently and inexpensively be used with a large variety of microtitre dishes.

There is a further need for apparatus useful in simultaneously conducting a laboratory procedure on a multiplicity of samples which does not require an excessive amount of laboratory work space.

Still further, there is a need for a fully automated machine which can simply, reliably and inexpensively conduct a series of laboratory tests on a multiplicity of liquid samples without requiring an excessive amount of work space.

SUMMARY

The invention satisfies these needs. The invention is a vacuum manifold useful in combination with first and second liquid receptacles, such as microtitre dishes. The invention comprises:

(a) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed

relationship such that the first receptacle can be fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle; and

(c) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base.

Typically, the vacuum means comprises a port defined within the base.

Both the base and the adapter frame can be sized and dimensioned to handle a wide variety of liquid receptacles.

In one typical embodiment, the second receptacle is adapted for filtration, its bottom comprising a filtration material.

Typically, both the first and second liquid receptacles complies a plurality of separate "wells." This facilitates the simultaneous processing of a large number of individual liquid samples in a single step.

The invention can also comprise stacking trays for retaining unused liquid receptacles and frames when not in use.

The invention is easily adaptable in a semi-automated or fully-automated machine having a computerized mechanical manipulator. Typically, the mechanical manipulator is programmed to robotically configure and reconfigure the various elements of the vacuum manifold to serially carry out a number of laboratory manipulations of a large number of individual liquid samples.

The invention can be conveniently and easily used to perform a wide variety of vacuum-assisted laboratory procedures, such as filtration, drying, column purification and column chromatography. The invention is inexpensive and simple to manufacture and operate, and its use conserves valuable laboratory work space.

DESCRIPTION OF THE DRAWINGS

These and other features, aspects and advantages of the present invention will become better understood with reference to the following description, appended claims and accompanying drawings where:

FIGURE 1 is an exploded perspective view showing a vacuum manifold having features of the invention and adapted for use with a narrow dish microtitre tray;

FIGURE 2 is an exploded cross-sectional view of the vacuum manifold shown in FIG. 1;

FIGURE 3 is a cross-sectional side view of the fully assembled vacuum manifold shown in FIG. 1;

FIGURE 4 is an exploded perspective view showing a vacuum manifold having features of the invention and adapted for use with a deep dish microtitre tray;

FIGURE 5 is an exploded cross-sectional view of the vacuum manifold shown in FIG. 4;

FIGURE 6 is a cross-sectional side view of the fully assembled vacuum manifold shown in FIG. 4;

FIGURE 7 is an exploded perspective view of a stacking tray assembly having features of the invention;

FIGURE 8 is an exploded cross-sectional view of the stacking tray assembly shown in FIG. 7;

FIGURE 9 is a cross-sectional view of the fully assembled stacking tray assembly shown in FIG. 7; and

FIGURE 10 is a perspective view of a machine and a kit having features of the invention.

DETAILED DESCRIPTION

The following discussion describes in detail one embodiment of the invention and several variations of that embodiment. This discussion should not be construed, however, as limiting the invention to those particular embodiments. Practitioners skilled in the art will recognize numerous other embodiments as well. For a definition of the complete scope of the invention, the reader is directed to the appended claims.

As shown in Figures 1-6, the vacuum manifold of the invention **10** comprises a base **12**, an adapter frame **14** and a means for drawing a vacuum.

The base has a bottom wall **16** and side walls **18**. The side walls **18** have uppermost portions **20** which cooperate to form a base wall perimeter **22**. The base **12** is sized and dimensioned to accept and retain a first liquid receptacle **24**.

Typically, the base **12** has a foot print with an area smaller than about 200 square centimeters. As used herein, the term "footprint" is meant to indicate the horizontal area and dimensions of various elements of the invention **10**.

In the embodiment of the invention shown in the drawings, the base **12** further comprises a vacuum port **26** capable of attachment to an external source of vacuum, such as a laboratory vacuum line. Typically, the vacuum port **26** is defined in the side walls **18** proximate to the bottom wall **16**. In embodiments having such a vacuum port **26**, a discontinuous lip **28** is provided to support the first receptacle **24** above and spaced-apart from the bottom wall **16**. This allows a vacuum generated using the vacuum port **26** to be uniform across the bottom wall **16**.

The base **12** can be made out of a wide variety of suitable materials, such as metals and plastics. For ease and inexpense of manufacture, the base **12** is typically made from a plastic.

In a typical embodiment, the base **12** has a rectangular footprint with the width between about 10 and about 13 centimeters and a length between about 12 and about 16 centimeters.

The base **12** is inexpensively made with dimensions capable of accepting and retaining the footprint of any first receptacle **24** having a footprint smaller than the footprint of the base **12**.

The adapter frame **14** is sized and dimensioned to accept a second liquid receptacle **30**. Typically, this is accomplished by providing the adapter frame **14** with an interior lip **32** capable of supporting the second receptacle **30** in a horizontal position. In the embodiments shown in the drawings, a sealing gasket **34** is disposed around the perimeter of the lip **28** to provide sufficient sealing of the second receptacle **30** to the adapter frame **14** when a vacuum is applied to the bottom side **36** of the second receptacle **30**.

The adapter frame **14** is further sized and dimensioned to attach to the base wall perimeter **22** of the base in a substantially sealed relationship such that, when a first receptacle **24** is disposed within the base **12** and a second receptacle **30** is disposed within the adapter frame **14**, the first receptacle **24** is fully enclosed within a chamber **38** formed by the base **12**, the adapter frame **14** and the second receptacle **30**.

Typically, the adapter frame **14** is rectangular with substantially the same footprint as that of the base **12**. The adapter frame **14** defines a central opening **40** which is sized and dimensioned to accept and retain the footprint of a particular second receptacle **30**.

The invention allows the use of a second receptacle **30** which has a different footprint than that of the first receptacle **24**. In the invention, this is

easily accomplished by adapting the base **12** to accept and retain the footprint of the first receptacle **24** and adapting the adaptor frame **14** to accept and retain the different footprint of the second receptacle **30**.

Similarly, the invention makes it easy to use liquid receptacles **24** and **30** of differing height. The base **12** is sized and dimensioned to accept and retain the first receptacle **24** having a given height while the adapter frame **14** is sized and dimensioned to accept a second receptacle **30** having a different height. Figures 4-6 illustrate the invention using an adapter frame **14** sized and dimensioned to accept and retain a typical deep well microtitre plate.

Like the base **12**, the adapter frame **14** can be made from a wide variety of suitable materials. Metals and plastics are easily used. Plastics are generally the preferred material because of the ease and inexpense of its use in the manufacturing process.

In the embodiment shown in the drawings, locator pins **42** are disposed within the base **12** and adapted to cooperate with matching holes **44** within the adapter frame **14** to facilitate the proper alignment and sealing of the adapter frame **14** to the base **12**.

In another embodiment (not shown in the drawings), the base **12** and the adapter frame **14** have matching beveled walls so that the adapter frame **14** "nests" with the base **12**.

The invention **10** can further comprise a first receptacle **24**, such as a microtitre dish, disposed within the base **12**. Similarly, the invention **10** can

comprise a second receptacle **30**, such as a microtitre dish, disposed within the adapter frame **14** above the first receptacle **24**.

In the embodiments shown in the drawings, the receptacles **24** and **30** are microtitre dishes having a plurality of separate wells **46** disposed in fixed arrays. For most applications, the fixed array of the second receptacle **30** is similar in layout to the fixed array of the first receptacle **24**. This allows each well **46** in the second receptacle **30** to discharge liquid into a corresponding well **46** in the first receptacle **24**. This is commonly the case, for example, in filtration processes using the invention **10**. In such filtration processes, the bottoms **48** of each separate well **46** of the second receptacle **30** comprise a filter material, such as a filtering membrane. As liquid is filtered from a well **46** in the second receptacle **30** across the filter membrane in the well bottom **48**, the liquid drops by gravity into the corresponding well **46** in the first receptacle **24**.

The vacuum means is for drawing a vacuum on the bottom side **36** of the second receptacle **30** when the second receptacle **30** is disposed within the adapter frame **14** and the first receptacle **24** is disposed within the base **12**. The vacuum means is typically one or more ports disposed within the base **12** or adapter frame **14**. As discussed above, the embodiments illustrated in the drawings define a vacuum port **26** near the bottom wall **16** of the base **12**. In this embodiment, when the vacuum manifold of the invention **10** is fully assembled with first and second liquid receptacles **24** and **30** are in place, a uniform vacuum is drawn across the bottom wall **16** of the base **12**. This uniform vacuum propagates around the first receptacle **24** so as to result in a uniform vacuum across the bottom side **36** of the second receptacle **30**.

Those skilled in the art will appreciate that, where the invention **10** is to be used with liquid receptacles **24** and **30** having small, separate wells **46**, the distance between the first receptacle **24** and the second receptacle **30** must be carefully chosen in conjunction with the degree of vacuum to be used within the vacuum manifold **10** so as not to horizontally divert liquid dripping from the second receptacle **30** to the first receptacle **24**. Said another way, the degree of vacuum must be sufficiently small, given the distance between the bottom side **36** of the second receptacle **30** and the uppermost portion of the first receptacle **24**, so that liquid dripping from a specific well **46** in the second receptacle **30** falls precisely vertically into the corresponding well **46** within the first receptacle **24**. Should the degree of vacuum be excessive, liquid falling from the second receptacle **30** towards the first receptacle **24** may be diverted horizontally into a non-corresponding well **46** within the first receptacle **24**.

The invention is also a kit **50** comprising the vacuum manifold **10** described above, together with one or more stacking trays **52** which are sized and dimensioned to accept at least one of the receptacles **24** and **30**. In a typical embodiment, the stacking trays **52** are similar in design and construction to the base **12**. The stacking trays, however, have no vacuum ports **26**.

The purpose of the stacking trays **52** is to allow receptacles **24** and **30** and/or adapter frames **14** to be stacked at a single location when not in use. This stacking capability maximizes the use of precious horizontal laboratory bench area.

As shown in Figures 7-9, the kit can also provide additional adapter frames **14**, each sized and dimensioned to accept and retain receptacles **24** and **30** having different footprints and/or differing heights.

The invention **10** is conveniently used with semi-automated DNA purification equipment, such as BioMek 2000 purification equipment sold by Beckman Instruments, Inc. of Fullerton, California.

The vacuum manifold of the invention **10** is also conveniently adapted to a fully automatic machine **54** capable of robotically carrying out a number of laboratory manipulations to a plurality of individual liquid samples. Such a machine **54** comprises the vacuum manifold **10** described above and a computerized mechanical manipulator **56** having a moveable gripper tool **58**. The mechanical manipulator **56** is basically a computerized robotic device programmed to robotically manipulate the various elements of the vacuum manifold **10** to perform first one laboratory manipulation on a plurality of liquid samples, then reconfigure the vacuum manifold **10** to perform a second or more laboratory manipulations on those liquid samples. In such a machine **54**, one or more stacking trays **52** described above can be conveniently used to stack various elements of the invention **10** in between use. For example, as shown in Figure 10, a machine of the invention **54** comprises a vacuum manifold **10** and two stacking trays **52**. Such a machine **54** can conveniently perform five or more different laboratory manipulations using the vacuum manifold **10**. One of skill in the art will appreciate the relative lack of space required by the machine **54** because of the stacking capabilities of the component elements.

The machine of the invention **54** is relatively easy and inexpensive to construct and maintain. Because of the simplicity of its construction and operation, such a machine **54** has a very high reliability factor.

Any process that can use vacuum as a driving force can generally be adapted for use in the invention. Such processes include column chromatography, column-based purification methods, vacuum drawing and filtration. For example, the invention can be easily adapted to carrying out chromatography procedures. In this case, the second liquid receptacle would have a plurality of chromatography columns, each having a semi-permeable bottom to allow a vacuum below the bottom to operate on liquid within each column.

Having thus described the invention, it should be apparent that numerous structural modifications and adaptations may be resorted to without departing from the scope and fair meaning of the instant invention as set forth hereinabove and as described hereinbelow by the claims.

What is Claimed is:

A vacuum manifold device useful in combination with first and first liquid receptacles, wherein both receptacles have a bottom and an uppermost portion, the device comprising:

(a) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed relationship such that the first receptacle can be fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle; and

(c) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base.

2. The vacuum manifold device of claim 1 wherein the base has a footprint with an area smaller than about 200 sq.cm.

3. The vacuum manifold device of claim 1 wherein the base further comprises a lip capable of supporting the first receptacle above the bottom wall.

4. The vacuum manifold device of claim 1 wherein the base further comprises a port capable of attachment to a source of vacuum.

5. The vacuum manifold device of claim 1 wherein the adapter frame further comprises a lip capable of supporting the second receptacle.

6. The vacuum manifold device of claim 1 wherein the base is sized and dimensioned to accept and retain a first receptacle having a first footprint and the adapter frame is sized and dimensioned to accept and retain a second receptacle having a different footprint.

7. The vacuum manifold device of claim 1 wherein the base is sized and dimensioned to accept and retain a first receptacle having a first height and the adapter frame is sized and dimensioned to accept and retain a second receptacle having a different height.

8. The vacuum manifold device of claim 1 further comprising a first receptacle disposed within the base and a second receptacle disposed within the adapter frame above the first receptacle.

9. The vacuum manifold device of claim 8 wherein the second receptacle has a footprint with dimensions different than those of the first receptacle.

10. The vacuum manifold device of claim 8 wherein the second receptacle has a height different than that of the first receptacle.

11. The vacuum manifold device of claim 8 wherein the bottom of the second receptacle comprises a filtration material.

12. The vacuum manifold device of claim 8 wherein the second receptacle comprises a plurality of separate wells.

13. The vacuum manifold device of claim 8 wherein the second receptacle comprises a plurality of separate wells disposed in a fixed array and the first receptacle comprises a plurality of separate wells disposed in a similar fixed array.

14. The vacuum manifold device of claim 8 wherein the second receptacle comprises a plurality of separate wells disposed in a fixed array, the bottoms of each separate well comprising a filter material, and the first receptacle comprises a plurality of separate wells disposed in a similar fixed array, the first receptacle being disposed immediately below the second receptacle.

15. The vacuum manifold device of claim 8 wherein the second receptacle and the first receptacle are microtitre plates.

16. A kit useful in carrying out multiple laboratory manipulations of a plurality of liquid samples using first and first liquid receptacles, wherein both receptacles have a bottom and an uppermost portion, the kit comprising:

(a) a base which is sized and dimensioned to accept and retain the second receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed

relationship such that the first receptacle can be fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle;

(c) a stacking tray which is sized and dimensioned to accept and retain at least one of the receptacles; and

(d) vacuum means for drawing a vacuum on the bottom of the first receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base.

17. The kit of claim 16 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a footprint different from the footprint of the other second receptacle.

18. The kit of claim 16 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a height different from the height of the other second receptacle.

19. A machine useful in carrying out multiple laboratory manipulations of a plurality of liquid samples using first and first liquid receptacles, wherein both receptacles have a bottom and an uppermost portion, the machine comprising:

(a) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed

relationship such that the first receptacle is fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle;

(c) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base; and

(d) a computerized mechanical manipulator having a moveable gripper tool, the mechanical manipulator being programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to perform at least one laboratory manipulation on at least one liquid sample.

20. The machine of claim 19 wherein the computerized mechanical manipulator is programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to perform a plurality of laboratory manipulations on at least one liquid sample.

21. The machine of claim 19 wherein the computerized mechanical manipulator is programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to simultaneously perform a plurality of laboratory manipulations on a plurality of liquid samples.

22. The machine of claim 19 wherein at least one of the manipulations comprises the simultaneous filtration of a plurality of liquid samples.

23. A combination useful in carrying out multiple laboratory manipulations of a plurality of liquid samples using first and first liquid

receptacles, wherein both receptacles have a bottom and an uppermost portion, the combination comprising:

(a) a machine comprising:

(2) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(3) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed relationship such that the first receptacle is fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle;

(4) a stacking tray which is sized and dimensioned to accept and retain one of the receptacles;

(5) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base; and

(6) a computerized mechanical manipulator having a moveable gripper tool, the mechanical manipulator being programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to perform at least one laboratory manipulation on at least one liquid sample; and

(b) a stacking tray which is sized and dimensioned to accept and retain at least one of the receptacles.

24. The combination of claim 23 further comprising a second stacking tray which is sized and dimensioned to accept and retain one of the receptacles.

25. The combination of claim 23 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a footprint different than the footprint of the other second receptacle.

26. The combination of claim 23 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a height different than the height of the other second receptacle.

FIG. 1

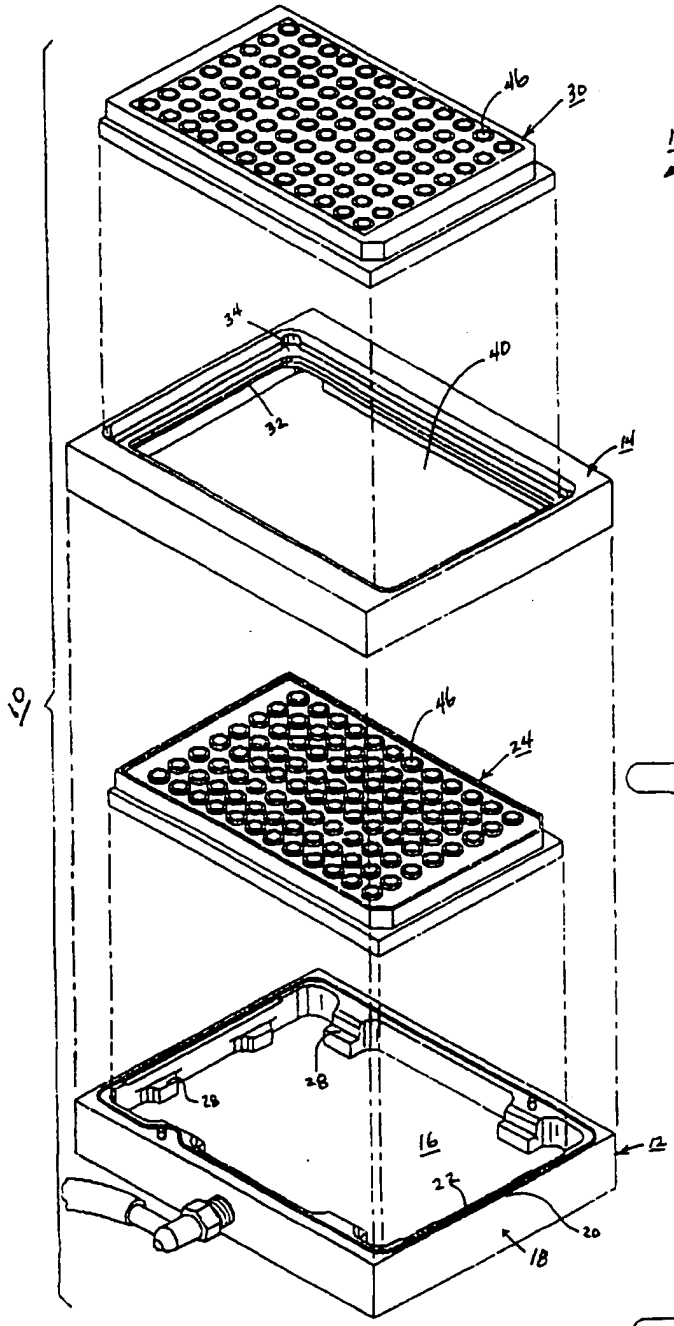


FIG. 2

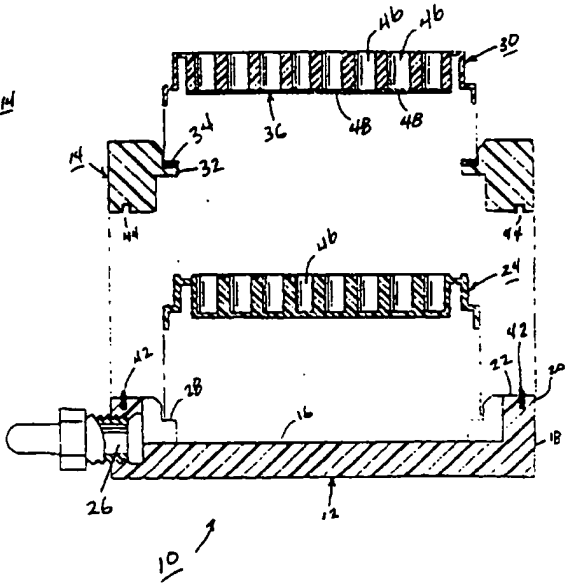


FIG. 3

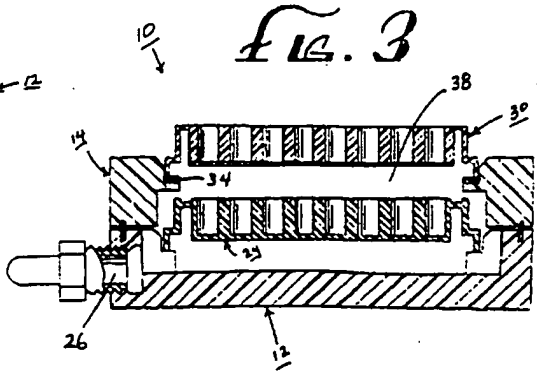


FIG. 4

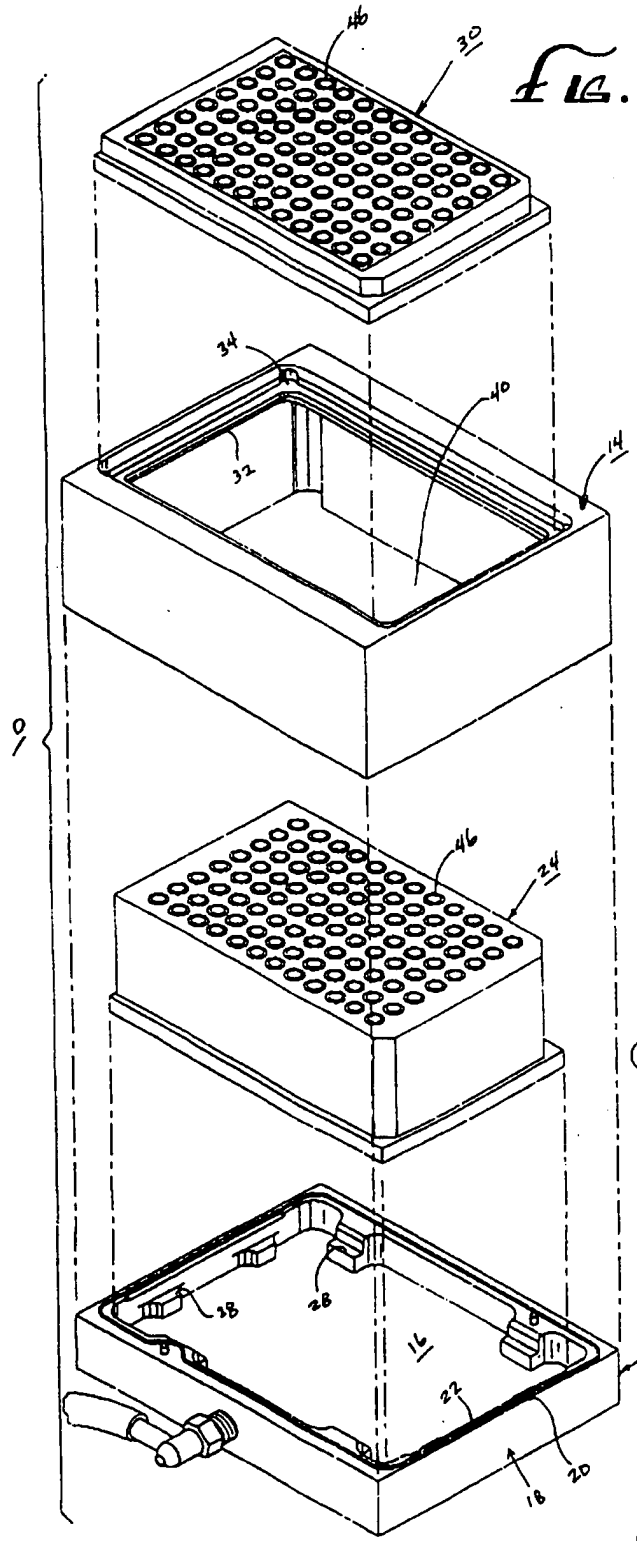


FIG. 5

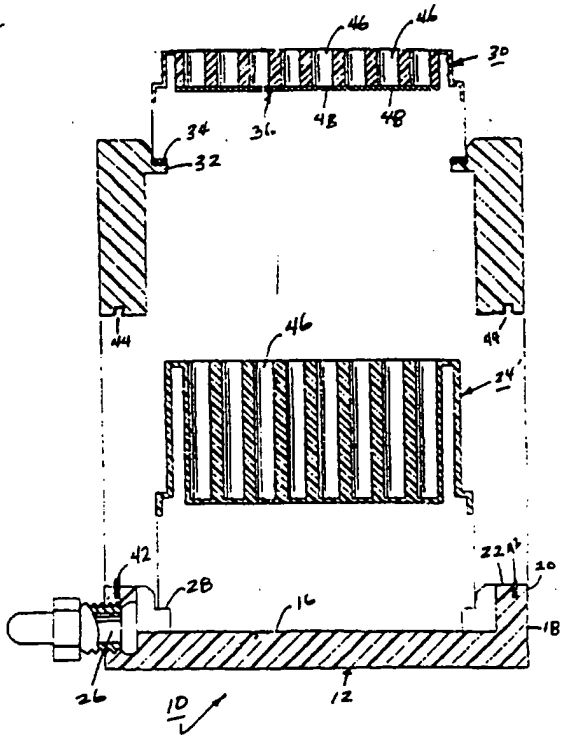


FIG. 6

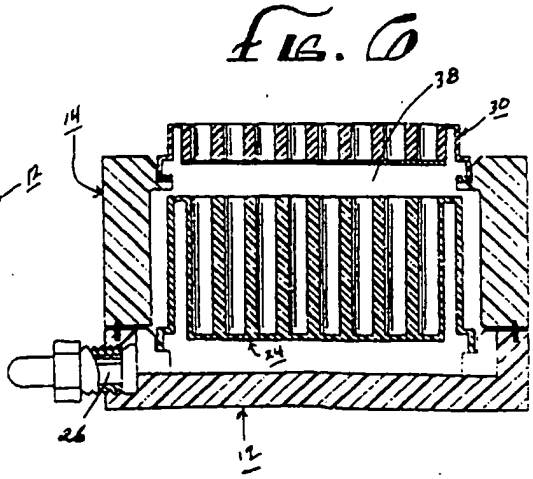


FIG. 7

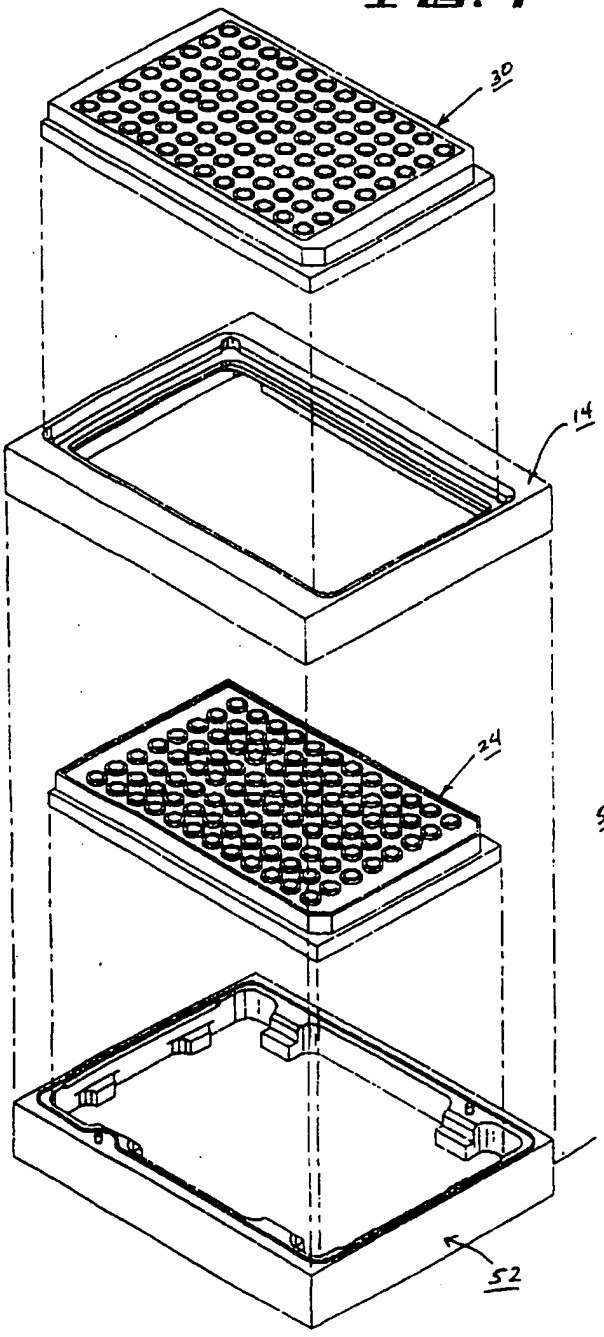


FIG. 8

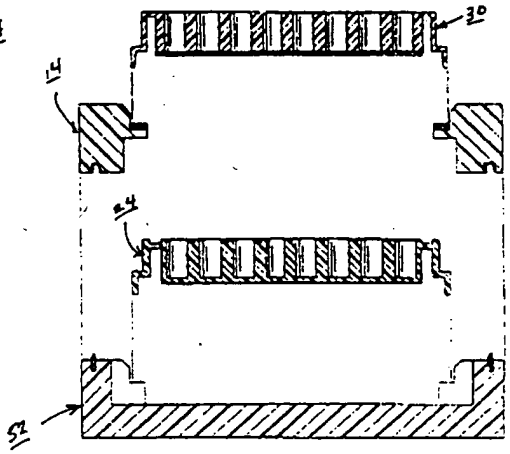
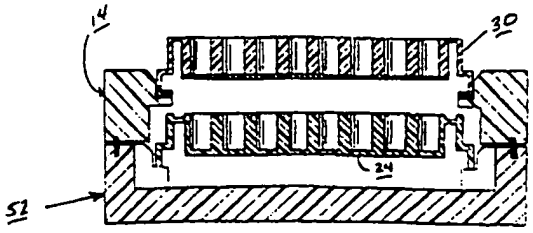


FIG. 9



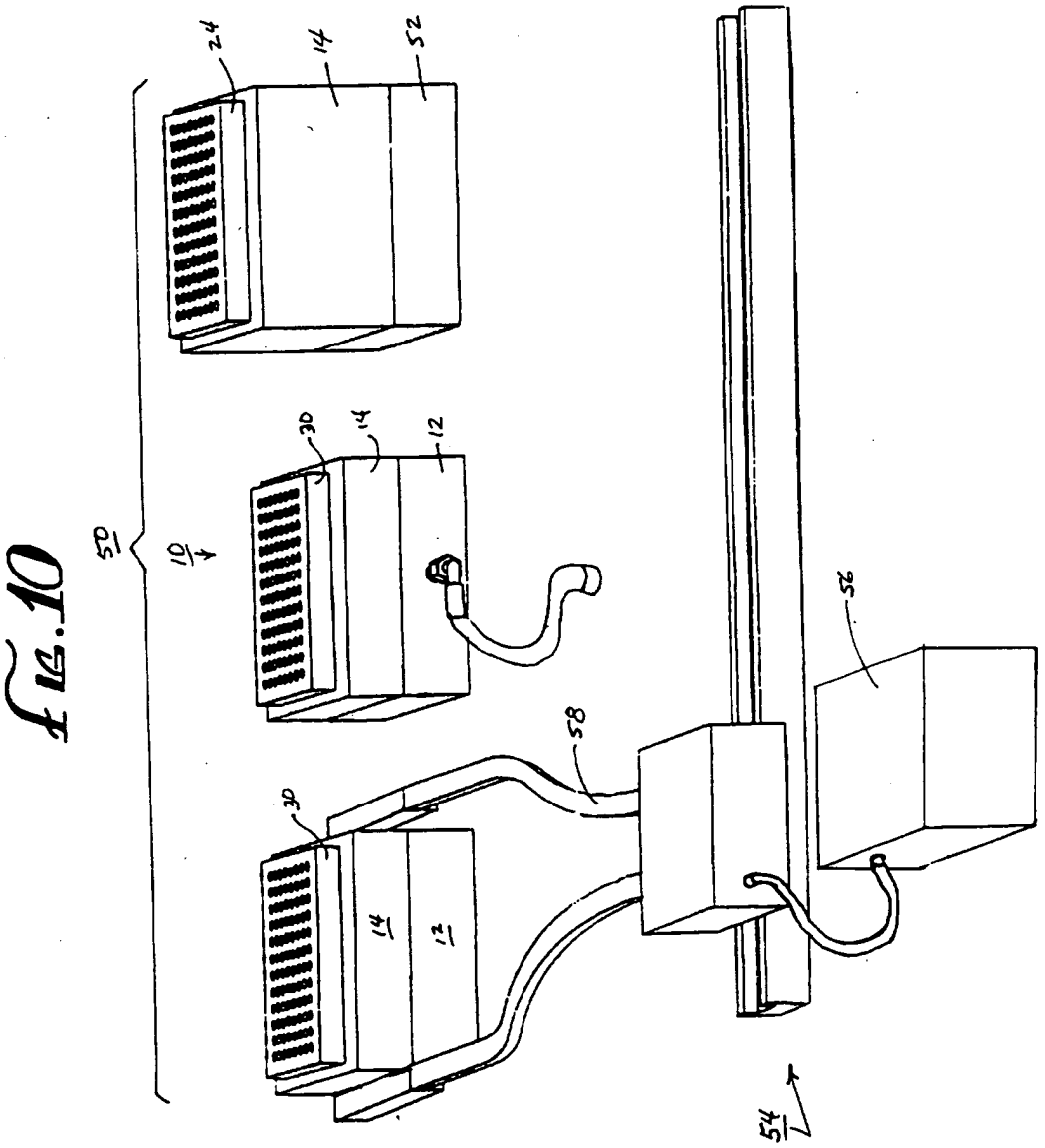


Fig. 10

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/13668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L3/00 G01N35/00 B01D61/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L G01N B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO,A,92 16294 (MINNESOTA MINING & MFG) 1 October 1992 see page 7, line 18 - page 8, line 4	1,2,4-15 3,16, 19-23
A	see page 14, line 34 - page 16, line 37; figures 5,6	17,18

Y	WO,A,92 02303 (PHARMACIA LKB BIOTECHNOLOGY AB) 20 February 1992 see page 6, line 3 - page 10, line 37; figures	16,19-23

Y	GB,A,2 246 081 (BIO RAD LABORATORIES) 22 January 1992 see page 4, line 9 - page 5, line 29; figures 1,4	3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 December 1996	13.12.96

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	see column 2, line 53 - column 3, line 4; figure 1	6
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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US-A-4300423	17-11-81	NONE		

CORRECTED VERSION*

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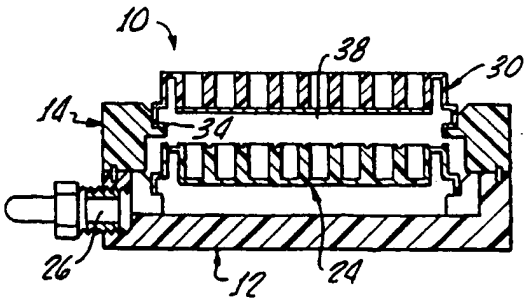
(54) Title: VACUUM MANIFOLD FOR LABORATORY PROCESSING OF MULTIPLE LIQUID SAMPLES

(57) Abstract

The invention provides a vacuum manifold which can be conveniently used in semi-automated and fully-automated laboratory machines to carry out a sequence of vacuum-assisted laboratory manipulations on a large number of individual liquid samples. The invention has a base (12) which is sized and dimensioned to accept and retain a first liquid receptacle (24), such as a microtitre dish. Generally, the base (12) has a bottom wall (16) and side walls (18) and the first receptacle (24) is designed to be retained within the side walls (18). The invention also has an adapter frame which is sized and dimensioned to accept and retain a second liquid receptacle (30), such as a second microtitre dish. The adapter frame (14) is typically a rectangular frame structure having a lip (32) which supports the second receptacle (30). The base (12) generally has a port (26) which is attachable to a source of vacuum. In operation, the first liquid receptacle (24) is placed within the base (12), the adapter frame (14) is placed on top of the base (12) and the second liquid receptacle (30) is placed on the adapter frame (14) so that a second receptacle (30) is located directly above the first receptacle (24). When vacuum is applied to the base using the vacuum port (26), a uniform vacuum is drawn along the bottom of the second liquid receptacle (30) which provides a driving force which acts upon liquid within the second receptacle (30). In a typical operation, the bottom of the second receptacle (30) is a filtration membrane and the vacuum is used to draw liquid from the second receptacle (30) across the filtered membrane into the first receptacle (24). Because of its modular construction, the various elements of the vacuum frame are easily stacked in stacking frames disposed to one side of the vacuum manifold. This stacking capability allows a large number of vacuum-assisted laboratory operations to be carried out on multiple sets of liquid samples without the necessity of a large amount of horizontal lab bench area. The stacking capability also facilitates the adaption of the invention with robotic equipment to provide a fully-automated laboratory processing tool.



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VACUUM MANIFOLD FOR LABORATORY PROCESSING OF MULTIPLE LIQUID SAMPLES

FIELD OF THE INVENTION

This invention relates generally to vacuum manifold devices, and specifically, to vacuum manifold devices useful in the simultaneous laboratory processing of multiple liquid samples.

BACKGROUND

It has become a common practice in testing laboratories to carry out simple laboratory processing steps on multiple liquid samples at the same time, in a single apparatus. This practice has greatly increased the efficiency of testing laboratories, especially laboratories doing a large volume of routine test work.

The simultaneous testing of multiple liquid samples in a single apparatus is conducted with apparatus especially designed for this purpose. The most common piece of apparatus is a disposable tray having multiple individual

"wells." These trays, commonly called "microtitre dishes," are made by a large number of manufacturers in a variety of sizes and shapes. In practice, an individual liquid sample is placed within each of the wells, where it is manipulated as part of the testing process.

Recently, equipment manufacturers in the trade have begun marketing specially designed vacuum manifolds for use with microtitre dishes. Such manifolds allow the practitioner to carry out common laboratory processes in microtitre dishes using vacuum as assisting force. Examples of such practices are filtration, drying and chromatography processes.

Unfortunately, the vacuum manifolds presently useful with microtitre dishes are not completely satisfactory. One problem is that such prior art vacuum manifolds are designed to work with specific microtitre dishes of a particular size and shape. If a practitioner wishes to another his microtitre dish, one with a different height or "footprint," the practitioner must invest in another vacuum manifold, one designed specifically for such other microtitre dish.

Another problem arises from the fact that vacuum processes generally constitute only one of several other processes which any particular liquid sample is to be subjected to. Handling the microtitre dishes from one testing operation to another frequently takes up a great deal of laboratory bench area as the various microtitre dishes are set aside between process steps.

A third problem is that, because of the relative inflexibility of present-day vacuum manifolds, and the excessive amount of area required by present-day multiple testing operations, present-day vacuum manifolds are not

easily incorporated into fully automated machines capable of carrying out a multiplicity of laboratory procedures using a relatively small amount of work space.

Accordingly, there is a need for a vacuum manifold which can simply, conveniently and inexpensively be used with a large variety of microtitre dishes.

There is a further need for apparatus useful in simultaneously conducting a laboratory procedure on a multiplicity of samples which does not require an excessive amount of laboratory work space.

Still further, there is a need for a fully automated machine which can simply, reliably and inexpensively conduct a series of laboratory tests on a multiplicity of liquid samples without requiring an excessive amount of work space.

SUMMARY

The invention satisfies these needs. The invention is a vacuum manifold useful in combination with first and second liquid receptacles, such as microtitre dishes. The invention comprises:

(a) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed

relationship such that the first receptacle can be fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle; and

(c) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base.

Typically, the vacuum means comprises a port defined within the base.

Both the base and the adapter frame can be sized and dimensioned to handle a wide variety of liquid receptacles.

In one typical embodiment, the second receptacle is adapted for filtration, its bottom comprising a filtration material.

Typically, both the first and second liquid receptacles complies a plurality of separate "wells." This facilitates the simultaneous processing of a large number of individual liquid samples in a single step.

The invention can also comprise stacking trays for retaining unused liquid receptacles and frames when not in use.

The invention is easily adaptable in a semi-automated or fully-automated machine having a computerized mechanical manipulator. Typically, the mechanical manipulator is programmed to robotically configure and reconfigure the various elements of the vacuum manifold to serially carry out a number of laboratory manipulations of a large number of individual liquid samples.

The invention can be conveniently and easily used to perform a wide variety of vacuum-assisted laboratory procedures, such as filtration, drying, column purification and column chromatography. The invention is inexpensive and simple to manufacture and operate, and its use conserves valuable laboratory work space.

DESCRIPTION OF THE DRAWINGS

These and other features, aspects and advantages of the present invention will become better understood with reference to the following description, appended claims and accompanying drawings where:

FIGURE 1 is an exploded perspective view showing a vacuum manifold having features of the invention and adapted for use with a narrow dish microtitre tray;

FIGURE 2 is an exploded cross-sectional view of the vacuum manifold shown in FIG. 1;

FIGURE 3 is a cross-sectional side view of the fully assembled vacuum manifold shown in FIG. 1;

FIGURE 4 is an exploded perspective view showing a vacuum manifold having features of the invention and adapted for use with a deep dish microtitre tray;

FIGURE 5 is an exploded cross-sectional view of the vacuum manifold shown in FIG. 4;

FIGURE 6 is a cross-sectional side view of the fully assembled vacuum manifold shown in FIG. 4;

FIGURE 7 is an exploded perspective view of a stacking tray assembly having features of the invention;

FIGURE 8 is an exploded cross-sectional view of the stacking tray assembly shown in FIG. 7;

FIGURE 9 is a cross-sectional view of the fully assembled stacking tray assembly shown in FIG. 7; and

FIGURE 10 is a perspective view of a machine and a kit having features of the invention.

DETAILED DESCRIPTION

The following discussion describes in detail one embodiment of the invention and several variations of that embodiment. This discussion should not be construed, however, as limiting the invention to those particular embodiments. Practitioners skilled in the art will recognize numerous other embodiments as well. For a definition of the complete scope of the invention, the reader is directed to the appended claims.

As shown in Figures 1-6, the vacuum manifold of the invention **10** comprises a base **12**, an adapter frame **14** and a means for drawing a vacuum.

The base has a bottom wall **16** and side walls **18**. The side walls **18** have uppermost portions **20** which cooperate to form a base wall perimeter **22**. The base **12** is sized and dimensioned to accept and retain a first liquid receptacle **24**.

Typically, the base **12** has a foot print with an area smaller than about 200 square centimeters. As used herein, the term "footprint" is meant to indicate the horizontal area and dimensions of various elements of the invention **10**.

In the embodiment of the invention shown in the drawings, the base **12** further comprises a vacuum port **26** capable of attachment to an external source of vacuum, such as a laboratory vacuum line. Typically, the vacuum port **26** is defined in the side walls **18** proximate to the bottom wall **16**. In embodiments having such a vacuum port **26**, a discontinuous lip **28** is provided to support the first receptacle **24** above and spaced-apart from the bottom wall **16**. This allows a vacuum generated using the vacuum port **26** to be uniform across the bottom wall **16**.

The base **12** can be made out of a wide variety of suitable materials, such as metals and plastics. For ease and inexpense of manufacture, the base **12** is typically made from a plastic.

In a typical embodiment, the base **12** has a rectangular footprint with the width between about 10 and about 13 centimeters and a length between about 12 and about 16 centimeters.

The base **12** is inexpensively made with dimensions capable of accepting and retaining the footprint of any first receptacle **24** having a footprint smaller than the footprint of the base **12**.

The adapter frame **14** is sized and dimensioned to accept a second liquid receptacle **30**. Typically, this is accomplished by providing the adapter frame **14** with an interior lip **32** capable of supporting the second receptacle **30** in a horizontal position. In the embodiments shown in the drawings, a sealing gasket **34** is disposed around the perimeter of the lip **28** to provide sufficient sealing of the second receptacle **30** to the adapter frame **14** when a vacuum is applied to the bottom side **36** of the second receptacle **30**.

The adapter frame **14** is further sized and dimensioned to attach to the base wall perimeter **22** of the base in a substantially sealed relationship such that, when a first receptacle **24** is disposed within the base **12** and a second receptacle **30** is disposed within the adapter frame **14**, the first receptacle **24** is fully enclosed within a chamber **38** formed by the base **12**, the adapter frame **14** and the second receptacle **30**.

Typically, the adapter frame **14** is rectangular with substantially the same footprint as that of the base **12**. The adapter frame **14** defines a central opening **40** which is sized and dimensioned to accept and retain the footprint of a particular second receptacle **30**.

The invention allows the use of a second receptacle **30** which has a different footprint than that of the first receptacle **24**. In the invention, this is

easily accomplished by adapting the base **12** to accept and retain the footprint of the first receptacle **24** and adapting the adaptor frame **14** to accept and retain the different footprint of the second receptacle **30**.

Similarly, the invention makes it easy to use liquid receptacles **24** and **30** of differing height. The base **12** is sized and dimensioned to accept and retain the first receptacle **24** having a given height while the adapter frame **14** is sized and dimensioned to accept a second receptacle **30** having a different height. Figures 4-6 illustrate the invention using an adapter frame **14** sized and dimensioned to accept and retain a typical deep well microtitre plate.

Like the base **12**, the adapter frame **14** can be made from a wide variety of suitable materials. Metals and plastics are easily used. Plastics are generally the preferred material because of the ease and inexpense of its use in the manufacturing process.

In the embodiment shown in the drawings, locator pins **42** are disposed within the base **12** and adapted to cooperate with matching holes **44** within the adapter frame **14** to facilitate the proper alignment and sealing of the adapter frame **14** to the base **12**.

In another embodiment (not shown in the drawings), the base **12** and the adapter frame **14** have matching beveled walls so that the adapter frame **14** "nests" with the base **12**.

The invention **10** can further comprise a first receptacle **24**, such as a microtitre dish, disposed within the base **12**. Similarly, the invention **10** can

comprise a second receptacle **30**, such as a microtitre dish, disposed within the adapter frame **14** above the first receptacle **24**.

In the embodiments shown in the drawings, the receptacles **24** and **30** are microtitre dishes having a plurality of separate wells **46** disposed in fixed arrays. For most applications, the fixed array of the second receptacle **30** is similar in layout to the fixed array of the first receptacle **24**. This allows each well **46** in the second receptacle **30** to discharge liquid into a corresponding well **46** in the first receptacle **24**. This is commonly the case, for example, in filtration processes using the invention **10**. In such filtration processes, the bottoms **48** of each separate well **46** of the second receptacle **30** comprise a filter material, such as a filtering membrane. As liquid is filtered from a well **46** in the second receptacle **30** across the filter membrane in the well bottom **48**, the liquid drops by gravity into the corresponding well **46** in the first receptacle **24**.

The vacuum means is for drawing a vacuum on the bottom side **36** of the second receptacle **30** when the second receptacle **30** is disposed within the adapter frame **14** and the first receptacle **24** is disposed within the base **12**. The vacuum means is typically one or more ports disposed within the base **12** or adapter frame **14**. As discussed above, the embodiments illustrated in the drawings define a vacuum port **26** near the bottom wall **16** of the base **12**. In this embodiment, when the vacuum manifold of the invention **10** is fully assembled with first and second liquid receptacles **24** and **30** are in place, a uniform vacuum is drawn across the bottom wall **16** of the base **12**. This uniform vacuum propagates around the first receptacle **24** so as to result in a uniform vacuum across the bottom side **36** of the second receptacle **30**.

Those skilled in the art will appreciate that, where the invention **10** is to be used with liquid receptacles **24** and **30** having small, separate wells **46**, the distance between the first receptacle **24** and the second receptacle **30** must be carefully chosen in conjunction with the degree of vacuum to be used within the vacuum manifold **10** so as not to horizontally divert liquid dripping from the second receptacle **30** to the first receptacle **24**. Said another way, the degree of vacuum must be sufficiently small, given the distance between the bottom side **36** of the second receptacle **30** and the uppermost portion of the first receptacle **24**, so that liquid dripping from a specific well **46** in the second receptacle **30** falls precisely vertically into the corresponding well **46** within the first receptacle **24**. Should the degree of vacuum be excessive, liquid falling from the second receptacle **30** towards the first receptacle **24** may be diverted horizontally into a non-corresponding well **46** within the first receptacle **24**.

The invention is also a kit **50** comprising the vacuum manifold **10** described above, together with one or more stacking trays **52** which are sized and dimensioned to accept at least one of the receptacles **24** and **30**. In a typical embodiment, the stacking trays **52** are similar in design and construction to the base **12**. The stacking trays, however, have no vacuum ports **26**.

The purpose of the stacking trays **52** is to allow receptacles **24** and **30** and/or adapter frames **14** to be stacked at a single location when not in use. This stacking capability maximizes the use of precious horizontal laboratory bench area.

As shown in Figures 7-9, the kit can also provide additional adapter frames **14**, each sized and dimensioned to accept and retain receptacles **24** and **30** having different footprints and/or differing heights.

The invention **10** is conveniently used with semi-automated DNA purification equipment, such as BioMek 2000 purification equipment sold by Beckman Instruments, Inc. of Fullerton, California.

The vacuum manifold of the invention **10** is also conveniently adapted to a fully automatic machine **54** capable of robotically carrying out a number of laboratory manipulations to a plurality of individual liquid samples. Such a machine **54** comprises the vacuum manifold **10** described above and a computerized mechanical manipulator **56** having a moveable gripper tool **58**. The mechanical manipulator **56** is basically a computerized robotic device programmed to robotically manipulate the various elements of the vacuum manifold **10** to perform first one laboratory manipulation on a plurality of liquid samples, then reconfigure the vacuum manifold **10** to perform a second or more laboratory manipulations on those liquid samples. In such a machine **54**, one or more stacking trays **52** described above can be conveniently used to stack various elements of the invention **10** in between use. For example, as shown in Figure 10, a machine of the invention **54** comprises a vacuum manifold **10** and two stacking trays **52**. Such a machine **54** can conveniently perform five or more different laboratory manipulations using the vacuum manifold **10**. One of skill in the art will appreciate the relative lack of space required by the machine **54** because of the stacking capabilities of the component elements.

The machine of the invention **54** is relatively easy and inexpensive to construct and maintain. Because of the simplicity of its construction and operation, such a machine **54** has a very high reliability factor.

Any process that can use vacuum as a driving force can generally be adapted for use in the invention. Such processes include column chromatography, column-based purification methods, vacuum drawing and filtration. For example, the invention can be easily adapted to carrying out chromatography procedures. In this case, the second liquid receptacle would have a plurality of chromatography columns, each having a semi-permeable bottom to allow a vacuum below the bottom to operate on liquid within each column.

Having thus described the invention, it should be apparent that numerous structural modifications and adaptations may be resorted to without departing from the scope and fair meaning of the instant invention as set forth hereinabove and as described hereinbelow by the claims.

What is Claimed is:

A vacuum manifold device useful in combination with first and first liquid receptacles, wherein both receptacles have a bottom and an uppermost portion, the device comprising:

(a) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed relationship such that the first receptacle can be fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle; and

(c) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base.

2. The vacuum manifold device of claim 1 wherein the base has a footprint with an area smaller than about 200 sq.cm.

3. The vacuum manifold device of claim 1 wherein the base further comprises a lip capable of supporting the first receptacle above the bottom wall.

4. The vacuum manifold device of claim 1 wherein the base further comprises a port capable of attachment to a source of vacuum.

5. The vacuum manifold device of claim 1 wherein the adapter frame further comprises a lip capable of supporting the second receptacle.

6. The vacuum manifold device of claim 1 wherein the base is sized and dimensioned to accept and retain a first receptacle having a first footprint and the adapter frame is sized and dimensioned to accept and retain a second receptacle having a different footprint.

7. The vacuum manifold device of claim 1 wherein the base is sized and dimensioned to accept and retain a first receptacle having a first height and the adapter frame is sized and dimensioned to accept and retain a second receptacle having a different height.

8. The vacuum manifold device of claim 1 further comprising a first receptacle disposed within the base and a second receptacle disposed within the adapter frame above the first receptacle.

9. The vacuum manifold device of claim 8 wherein the second receptacle has a footprint with dimensions different than those of the first receptacle.

10. The vacuum manifold device of claim 8 wherein the second receptacle has a height different than that of the first receptacle.

11. The vacuum manifold device of claim 8 wherein the bottom of the second receptacle comprises a filtration material.

12. The vacuum manifold device of claim 8 wherein the second receptacle comprises a plurality of separate wells.

13. The vacuum manifold device of claim 8 wherein the second receptacle comprises a plurality of separate wells disposed in a fixed array and the first receptacle comprises a plurality of separate wells disposed in a similar fixed array.

14. The vacuum manifold device of claim 8 wherein the second receptacle comprises a plurality of separate wells disposed in a fixed array, the bottoms of each separate well comprising a filter material, and the first receptacle comprises a plurality of separate wells disposed in a similar fixed array, the first receptacle being disposed immediately below the second receptacle.

15. The vacuum manifold device of claim 8 wherein the second receptacle and the first receptacle are microtitre plates.

16. A kit useful in carrying out multiple laboratory manipulations of a plurality of liquid samples using first and first liquid receptacles, wherein both receptacles have a bottom and an uppermost portion, the kit comprising:

(a) a base which is sized and dimensioned to accept and retain the second receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed

relationship such that the first receptacle can be fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle;

(c) a stacking tray which is sized and dimensioned to accept and retain at least one of the receptacles; and

(d) vacuum means for drawing a vacuum on the bottom of the first receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base.

17. The kit of claim 16 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a footprint different from the footprint of the other second receptacle.

18. The kit of claim 16 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a height different from the height of the other second receptacle.

19. A machine useful in carrying out multiple laboratory manipulations of a plurality of liquid samples using first and first liquid receptacles, wherein both receptacles have a bottom and an uppermost portion, the machine comprising:

(a) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(b) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed

relationship such that the first receptacle is fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle;

(c) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base; and

(d) a computerized mechanical manipulator having a moveable gripper tool, the mechanical manipulator being programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to perform at least one laboratory manipulation on at least one liquid sample.

20. The machine of claim 19 wherein the computerized mechanical manipulator is programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to perform a plurality of laboratory manipulations on at least one liquid sample.

21. The machine of claim 19 wherein the computerized mechanical manipulator is programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to simultaneously perform a plurality of laboratory manipulations on a plurality of liquid samples.

22. The machine of claim 19 wherein at least one of the manipulations comprises the simultaneous filtration of a plurality of liquid samples.

23. A combination useful in carrying out multiple laboratory manipulations of a plurality of liquid samples using first and first liquid

receptacles, wherein both receptacles have a bottom and an uppermost portion, the combination comprising:

(a) a machine comprising:

(2) a base which is sized and dimensioned to accept and retain the first receptacle, the base having a bottom wall and side walls, the side walls having uppermost portions which cooperate to form a base wall perimeter;

(3) an adapter frame which is sized and dimensioned to accept and retain the second receptacle, the adapter frame being further sized and dimensioned to attach to the base wall perimeter in substantially sealed relationship such that the first receptacle is fully enclosed within a chamber formed by the base, the adapter frame and the second receptacle;

(4) a stacking tray which is sized and dimensioned to accept and retain one of the receptacles;

(5) vacuum means for drawing a vacuum on the bottom of the second receptacle when the second receptacle is disposed within the adapter frame and the first receptacle is disposed within the base; and

(6) a computerized mechanical manipulator having a moveable gripper tool, the mechanical manipulator being programmed to robotically configure the base, the adapter frame, the stacking frame and the receptacles using the moveable gripper tool to perform at least one laboratory manipulation on at least one liquid sample; and

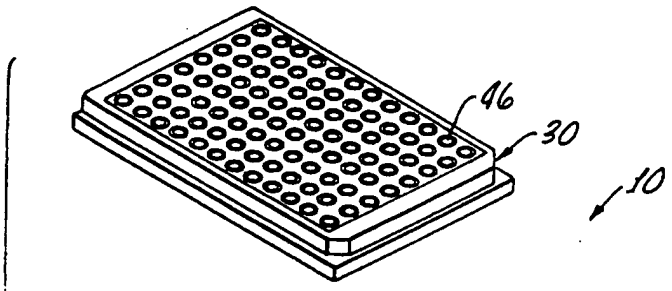
(b) a stacking tray which is sized and dimensioned to accept and retain at least one of the receptacles.

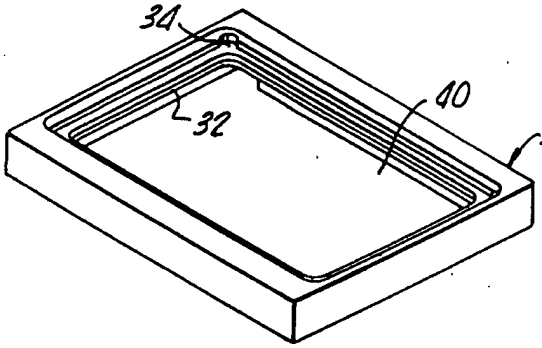
24. The combination of claim 23 further comprising a second stacking tray which is sized and dimensioned to accept and retain one of the receptacles.

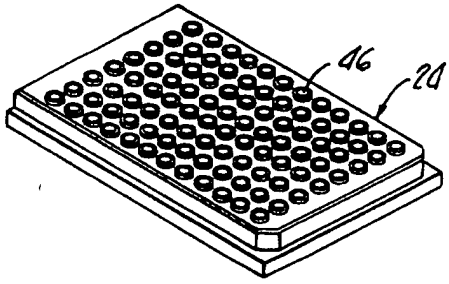
25. The combination of claim 23 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a footprint different than the footprint of the other second receptacle.

26. The combination of claim 23 further comprising a second adapter frame sized and dimensioned to accept and retain another second receptacle having a height different than the height of the other second receptacle.

FIG. 1.







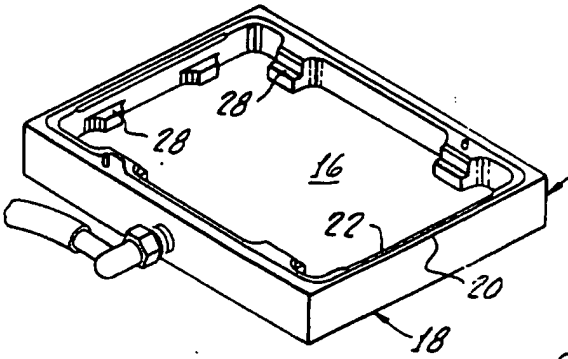


FIG. 2.

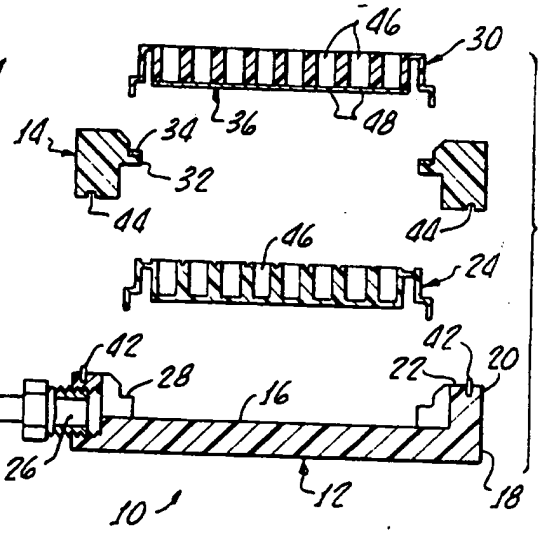


FIG. 3.

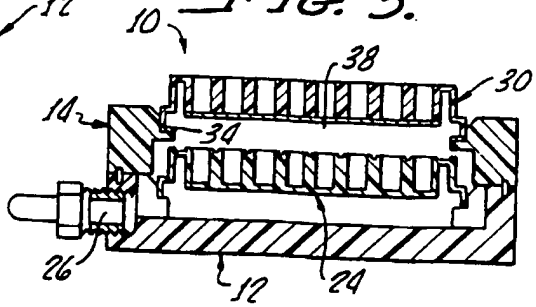


FIG. 4

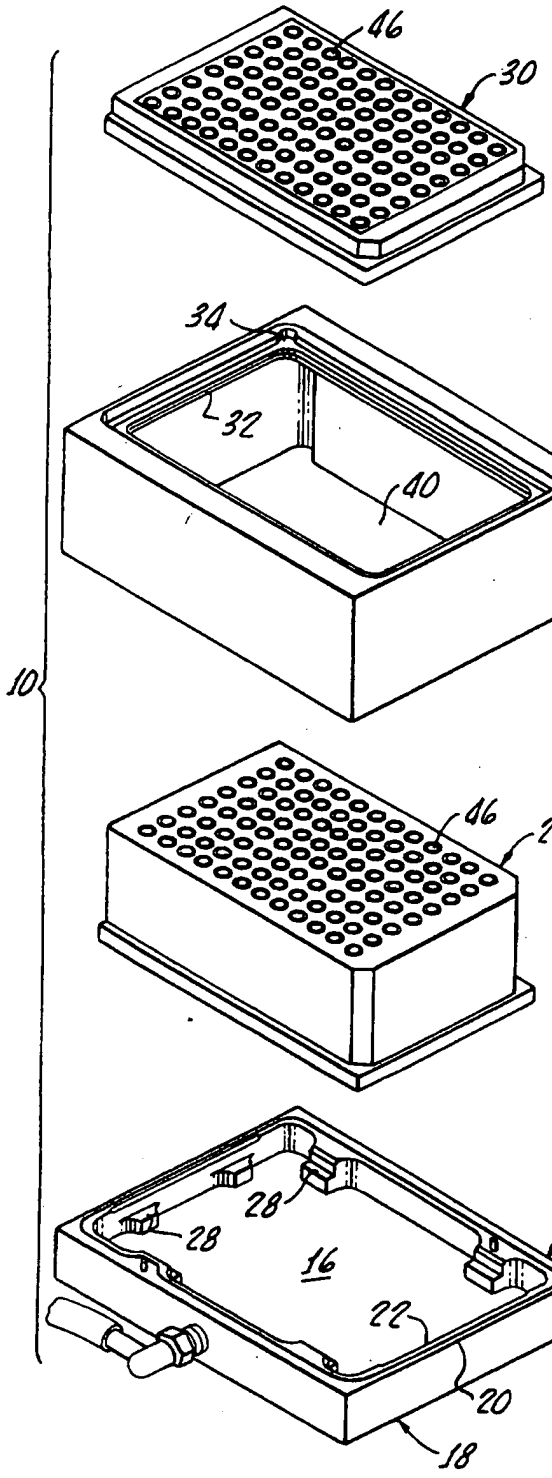


FIG. 5.

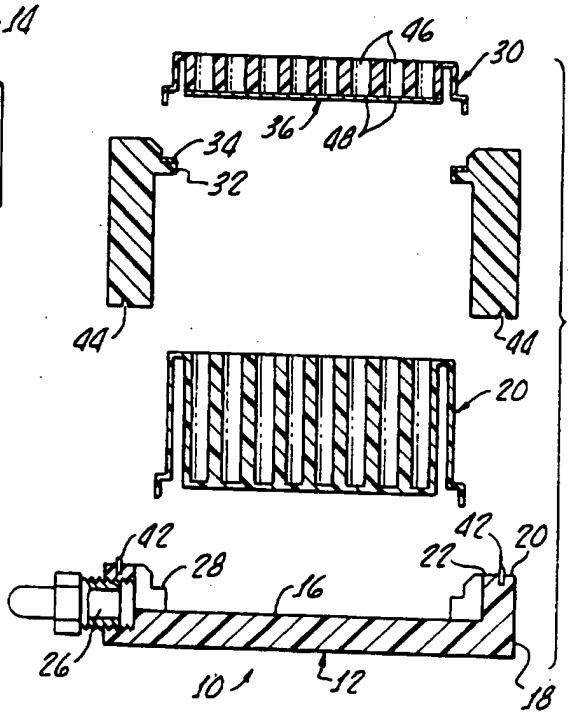


FIG. 6.

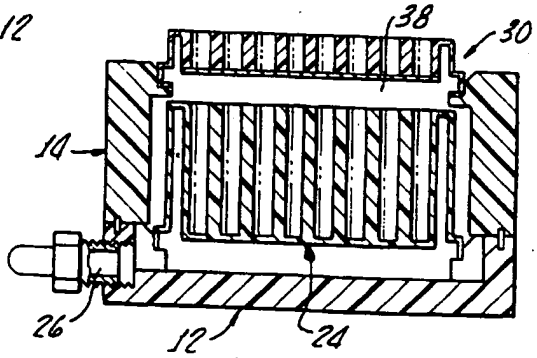


FIG. 7.

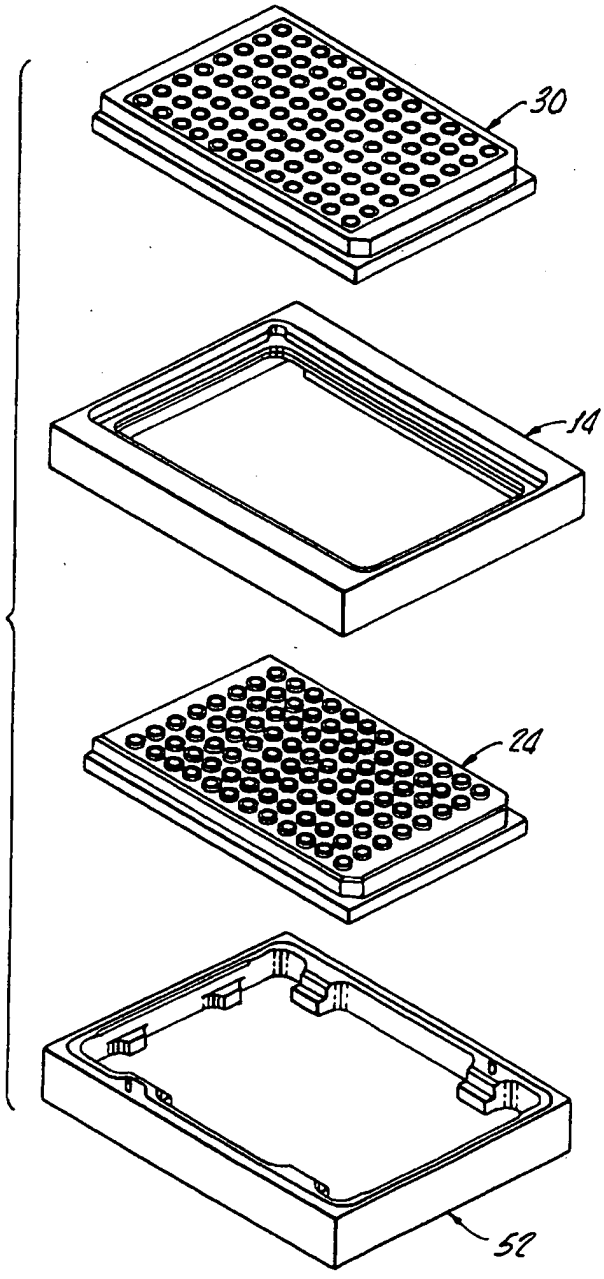


FIG. 8.

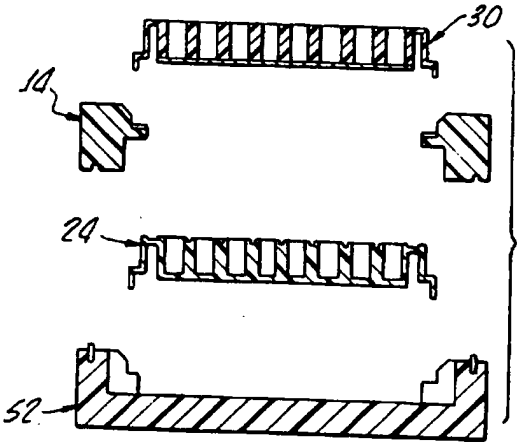
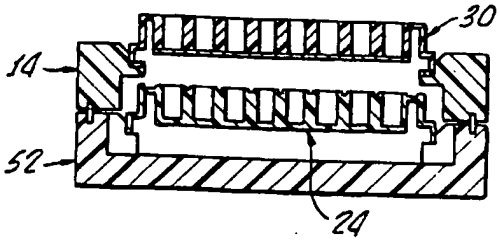


FIG. 9.



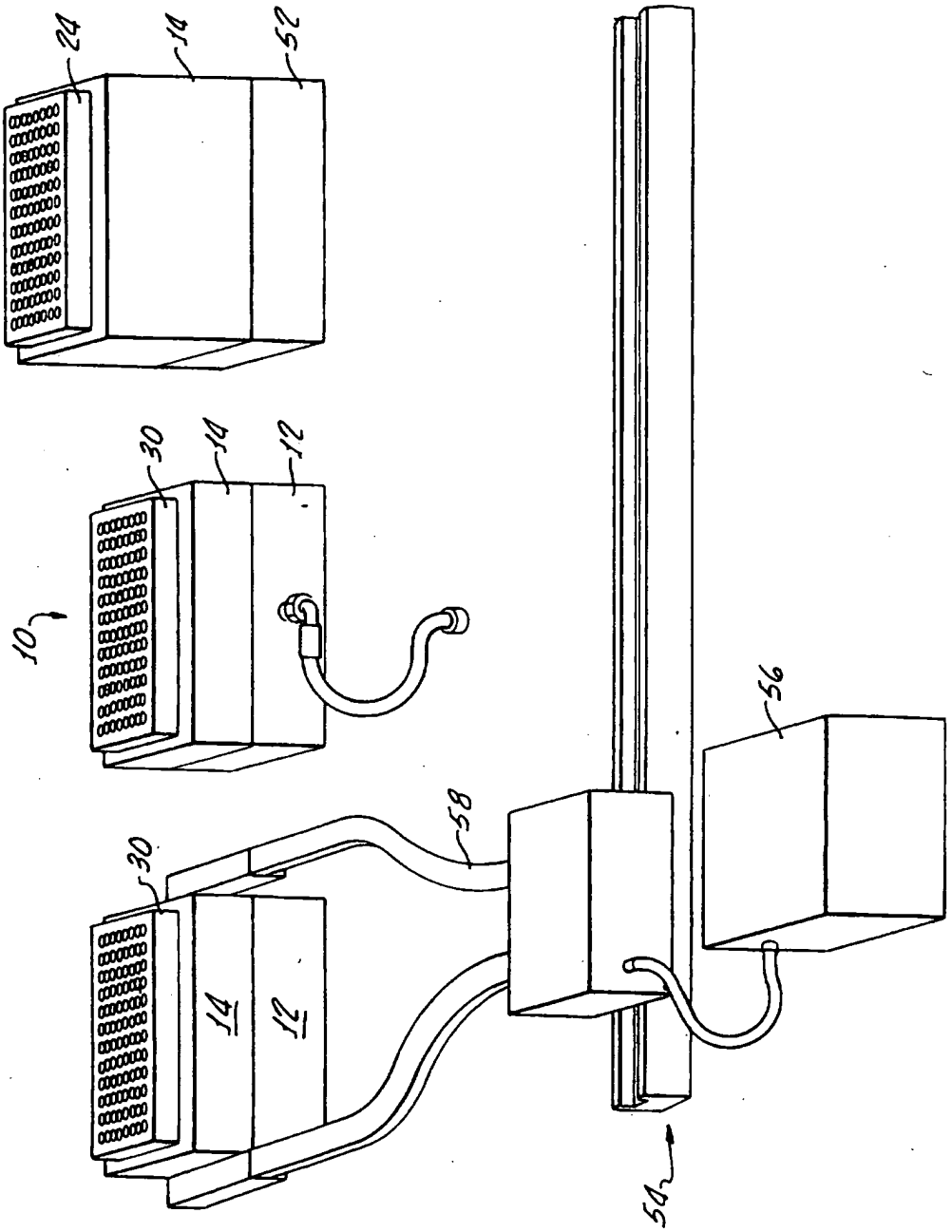


FIG. 10.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/13668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L3/00 G01N35/00 B01D61/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L G01N B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 16294 (MINNESOTA MINING & MFG) 1 October 1992	1,2,4-15
Y	see page 7, line 18 - page 8, line 4	3,16,
A	see page 14, line 34 - page 16, line 37; figures 5,6	19-23 17,18

Y	WO,A,92 02303 (PHARMACIA LKB BIOTECHNOLOGY AB) 20 February 1992 see page 6, line 3 - page 10, line 37; figures	16,19-23

Y	GB,A,2 246 081 (BIO RAD LABORATORIES) 22 January 1992 see page 4, line 9 - page 5, line 29; figures 1,4	3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 1996	13.12.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bindon, C

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INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 96/13668

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US,A,4 902 481 (CLARK PHILLIP ET AL) 20 February 1990 see column 2, line 53 - column 3, line 4; figure 1 ---	1,2 6
A	WO,A,93 19199 (CELSIS LIMITED) 30 September 1993 see page 9, line 22 - page 10, line 33 ---	1,6,7
A	US,A,4 300 423 (PRICE PAUL) 17 November 1981 see abstract; figure 3 -----	1,6,7

1

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Information on patent family members

Intn ·nal Application No
PCT/US 96/13668

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